Remarks

Claims 1-27 are pending in this application; claims 15-23 are currently withdrawn from examination. Applicants appreciate the Examiner's withdrawal of the § 112 and § 102 rejections made in the last Office action.

A. Response to the Examiner's Statement of the Invention

Applicants note the Examiner's summary of Applicants' invention. Applicants do not adopt the Examiner's summary of Applicants' invention as being either accurate or complete. Moreover, to the extent that the Examiner's summary suggests that the sole novelty of Applicants' claims resides in the use of a "presynthesized" reagent, Applicants disagree. The novelty of Applicants' claimed invention must be assessed by consideration of all the limitations of the claims in Applicants' application (now pending or as hereafter amended or added).

B. 35 U.S.C. § 103(a) rejections

The Examiner rejects claims 1-14 and 24-27 as allegedly being obvious over Weckwerth et al., when taken in combination with Gygi et al., or Aebersold et al. Applicants traverse these rejections.

Claims 1-13

Independent claim 1 recites a method of comparing the phosphorylation states of one or more proteins in two or more samples comprising, in part, providing a substantially chemically identical and differentially isotopically labeled protein reactive reagent wherein the protein reactive reagent satisfies the formula B-L-PhRG, wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that reacts with amino acid residues that were formerly phosphorylated. The claimed method additionally recites reacting each sample with one of the protein reactive reagents.

Weckwerth does not teach or suggest reacting a protein in a sample with a protein reactive reagent that satisfies the formula B-L-PhRG as recited in claim 1. Rather, Weckwerth discloses reacting an ethanethiol with one protein sample and deuterated ethanethiol with another protein sample so that the ethanethiol or deuterated ethanethiol attaches to the double bond of

dehydroalanine in the protein samples. The Weckwerth ethanethiol/dueterated ethanethiol does not include a binding agent, as is recited in claim 1. Further, Weckwerth does not teach or suggest that either ethanethiol group should include a binding agent. Clearly, Weckwerth does not render claim 1 obvious, as the Examiner has recognized.

Further, the Examiner's suggestion to combine Gygi or Aebersold with Weckwerth is improper. Weckwerth was aware of the Gygi publication as well as other Aebersold publications in the art that taught the isotope coded affinity tag (ICAT) method disclosed in the Gygi and Aebersold publications cited by the Examiner. (See Weckwerth, citations 2 and 12). If Applicants' claimed method were obvious, which it is not, Weckwerth would have taught or suggested the combination of its method with Gygi or Aebersold. At no point did Weckwerth suggest or even hint at the idea that a binding agent be used with its ethanethiols. Instead, Weckwerth teaches away from such a combination. Specifically, Weckwerth criticizes the use of binding agents in the ICAT methods taught in Gygi and Aebersold. (Weckwerth, p. 1677, bottom of first column – top of second column) ("Current ICAT methods use chemical attachment of biotin groups to cysteine peptide residues. Therefore, peptides bearing post-translational modifications will be lost during biotin/avidin affinity purification.") (emphasis added). As the Examiner knows, "[i]t is improper to combine references where the references teach away from their combination." MPEP § 2145 D.

Because there is no motivation to combine Weckwerth with Gygi or Aebersold, the Examiner has not shown that claim 1 is obvious; thus, claim 1 is allowable. Claims 2-13 are allowable at least because they depend from allowable claim 1 and because of each claim's unique and non-obvious combination of features.

Accordingly, Applicants request that the Examiner withdraw the § 103(a) rejections of claims 1-13.

Claim 14

Independent claim 14 recites a method for screening for a therapeutic agent that alters the phosphorylation state of a protein that comprises, in part, tagging a test sample and a control sample with a substantially chemically identical and differentially isotopically labeled protein reactive reagent wherein the protein reactive reagent satisfies the formula B-L-PhRG, wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or

more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that reacts with amino acid residues that were formerly phosphorylated.

The Examiner has not cited any publications that teach or suggest using Applicants' recited protein reactive reagent in a method of screening for phosphorylation altering therapeutic agents. "[T]he prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. For at least this reason (as well as those discussed above in relation to claim 1) claim 14 is patentable over the art of record.

Accordingly, Applicants request that the Examiner withdraw the § 103(a) rejection of claim 14.

Claims 24-27

Independent claim 24 recites a method of detecting more than one type of phosphorylated amino acid residue in a protein comprising, in part, removing the phosphate group from at least one serine residue or at least one threonine residue, removing the phosphate group from at least one tyrosine residue, and tagging the at least on serine residue or at least one threonine residue and the least one tyrosine residue with a substantially chemically identical and differentially isotopically labeled protein reactive reagent wherein the protein reactive reagent satisfies the formula B-L-PhRG, wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that reacts with amino acid residues that were formerly phosphorylated.

Neither Weckwerth, Gygi, nor Aebersold teach or suggest removing the phosphate group from a serine, threonine, or tyrosine residue and tagging the formerly phosphorylated residue with any group. Weckwerth is the only publication of the three that teaches phosphate removal from any protein, but Weckwerth only teaches or suggests the removal of a phosphate group from cysteine residues. "[T]he prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. For this reason alone, claim 24 is patentably nonobvious.

Moreover, the suggested combination of references is improper, and even if not improper, the suggested combination would not teach or suggest the method of claim 24 for the reasons discussed above in relation to claim 1.

Claim 24 is allowable for at least the reasons discussed above. Claims 25-27 are allowable at least because they depend from allowable claim 24 and also because of the claims' recitations of unique and non-obvious combinations of features.

Accordingly, Applicants request the Examiner withdraw the § 103(a) rejections of claims 24-27.

C. Conclusion

For at least the foregoing reasons, all of Applicants pending claims are allowable. Applicants request that the Examiner withdraw the § 103(a) rejections and allow all of Applicants' pending claims.

If the Examiner believes any further action would place this application in better condition for allowance, the Examiner is invited to telephone the undersigned at the telephone number provided below.

Respectfully submitted,

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